REMARKS

I. Detailed Action

A. Election/Restrictions

Applicants acknowledge that new claims 42-44, 46-48, and 50-53 are drawn to nonelected groups and are withdrawn.

B. Sequence Rules

Applicants thank the Examiner for pointing out the inadvertent mistake of not complying with the sequence rules outlined in 37 C.F.R. 1.821-1.825. Applicants are submitting a new CFR and paper copy of the sequence listing and ask that it be submitted into the record.

C. Specification

Applicants acknowledge that the Examiner has withdrawn the objection to the Specification in view of the amendment.

D. Double Patenting

Applicants acknowledge that the Examiner has withdrawn the rejection of the claims under the judicially created doctrine of obviousness-type double-patenting in view of the terminal disclaimer.

II. Claim Rejections – 35 U.S.C. § 112, First Paragraph

A. Written Description

Claims 1-3, 7-11, 14, 16-20, 26-29, 36-28, 40, 41, 45, 49, 54 and 55 stand rejected as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Examiner additionally states

that the "claims encompass a genus of nucleic acids which comprise prolactin receptor polymorphisms which are not disclosed in the specification" and "no common element or attributes of the sequences are disclosed which would permit selection of sequences as polymorphisms." The Examiner further states that "[n]o structural limitations or requirements which provide guidance on the identification of sequences which meet these functional limitations of associating a polymorphism with litter size is provided."

Applicants respectfully traverse this rejection. "A description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the Examiner to rebut the presumption." In re Marzocchi, 439 F.2d 220, 224 (CCPA 1971). The Examiner, therefore, must have a reasonable basis to challenge the adequacy of the written description. Id. The Examiner has the initial burden of presenting by a preponderance of the evidence why a person skilled in the art would not recognize in Applicants' disclosure a description of the invention defined by the claims. In re Wertheim, 541 F.2d 257, 262 (CCPA 1976). In rejecting claims, the Examiner must set forth express findings of fact regarding the above analysis which support the lack of written description conclusion. Id.

In this case, it is respectfully submitted that the Examiner has not met the initial burden of presenting evidence as to why a person skilled in the art would not recognize in Applicant's disclosure a description of other polymorphisms in the prolactin receptor gene which are indicative of increased litter size. Instead, the Examiner merely notes that "[t]his large genus is represented in the specification by only the particularly named four polymorphisms for which data is provided . . . ."

Applicants "are not required to disclose every species encompassed by their claims even in an unpredictable art". Regents of University of California v. Eli Lilly, 119 F.3d 1559, 1569

(Fed. Cir. 1997). The invention is an association of a particular gene with a phenotype in pigs. Applicants have demonstrated different and distinct polymorphisms that are so correlated. From this teaching, once a target gene has been successfully identified it takes no more than routine screening to identify other polymorphisms within the same gene. All claimed uses have the same underlying gene and the same trait. Although the specification does not explicitly list all other possible polymorphisms, it does state that one could use the method described in the specification to "evaluate pig DNA, genetically type individual pigs, and detect genetic differences in pigs. In particular, a sample of pig genomic DNA may be evaluated by reference to one or more controls to determine if a polymorphism in the prolactin receptor gene is present" (specification, p. 25).

In addition, the specification states, with regard to how one skilled in the art would determine if a polymorphism was present:

> "the prolactin receptor genotype of a pig may be determined by obtaining a sample of its genomic DNA, conducting RFLP analysis of the prolactin receptor gene in the DNA, and comparing the results with a control. Again, the control is the result of RFLP analysis of the prolactin receptor gene of a different pig. The results genetically type the pig by specifying the polymorphism in its prolactin receptor genes" (specification, p. 25).

Furthermore, the specification also states:

> "[a]s is well known to those of skill in the art, a variety of techniques may be utilized when comparing nucleic acid molecules for sequence differences. These include by way of example, restriction fragment length polymorphism analysis, heteroduplex analysis, single strand conformation polymorphism analysis, denaturing gradient electrophoresis and temperature gradient electrophoresis" (specification, p. 5).

As stated in the amended claim 1, this assay will be of the prolactin receptor gene as set forth in SEQ ID NO: 3. Thus, any polymorphism screened for will be a polymorphism of the gene sequence as set forth in SEQ ID NO: 3. As shown by the specification and the level of skill of

those in the art, Applicants are in possession of the common element or attributes of the sequences which would permit selection of the sequences as polymorphisms.

Moreover, Applicants have amended the claims to more specifically illustrate their possession of the claimed invention. Applicants have amended the independent claims by describing the claimed invention using the descriptive means of the structure (SEQ ID 3) of the prolactin receptor gene and function. Reference to "95% sequence identity" and "fragment thereof" have been removed, thereby making any argument as to whether Applicant is in possession of the sequence moot. All claims which lack structure have either been amended or cancelled. It is thus clear that Applicants have adequately described the polymorphisms described by the claims.

It is therefore respectfully submitted that the Examiner has failed to meet the requisite burden for showing a violation of the written description requirement. Applicants therefore respectfully request that this ground of rejection be withdrawn.

B. § 112, first paragraph: Enablement

Claims 1-3, 7-11, 14, 16-20, 26-29, 36-28, 40, 41, 45, 49, 54 and 55 stand rejected for lack of enablement. The Examiner states that the claims do not provide enablement for all polymorphisms, including the including the Msel polymorphism.

Applicants respectfully traverse this rejection. The test for enablement under § 112, first paragraph, is "whether or not the specification contains a sufficiently explicit disclosure to enable one having ordinary skill in the relevant field to practice the invention claimed therein without the exercise of undue experimentation." Ex Parte Forman, 230 U.S.P.Q. 546 (Bd. Pat. App. & Int'f 1986). As stated by the Examiner, several factors may be considered in determining

whether a specification is enabling. Although none of these factors are controlling and not all of them need be considered, they are illustrative: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The specification provides clear guidance as to how a polymorphism might be screened for in the prolactin receptor gene. As noted in the specification:

> Male and female pigs of the same breed or breed cross or derived from similar genetic lineages are mated. The number of offspring produced by each female pig is determined. RFLP analysis of the parental DNA is conducted as discussed above in order to determine polymorphisms in the prolactin receptor gene of each pig. The polymorphisms are associated with the number of offspring (specification, p. 22).

Applicants have identified a phenotype (increased litter size) that is associated with a certain genetic makeup (polymorphisms present in the prolactin gene as set forth in SEQ ID NO: 3). The methods of screening for these polymorphisms is well known to those skilled in the art, as is evidenced by the large number available:

> Any method of identifying the presence or absence of this marker may be used, including for example single-strand conformation polymorphism (SSCP) analysis, base excision sequence scanning (BESS), RFLP analysis, heteroduplex analysis, denaturing gradient gel electrophoresis, and temperature gradient electrophoresis, allelic PCR, ligase chain reaction direct sequencing, mini sequencing, nucleic acid hybridization, micro-array-type detection of the prolactin gene, or other linked sequences of the prolactin receptor gene and examination for the markers in the 3' translated and nontranslated region (specification, p. 10).

The guidance provided by the specification for identifying polymorphisms which are encompassed by the invention is clear and well understood by those skilled in the biotechnology field. As described by the specification, those skilled in the art would know to calculate the

number of offspring being produced by each female. A polymorphism is then identified using, for example, RFLP analysis of the parental DNA. This polymorphism may then be screened for using any of the many methods available. The specification therefore enables one skilled in the art to use and practice the invention by encompassing polymorphisms of the prolactin receptor gene, as set forth in SEQ ID No: 3, which are associated with increased litter size.

The Examiner next states that the specification demonstrates the unpredictability of the invention since the P values for the association of the MseI SNP with litter size are above conventional values.

Applicants have amended the claims to remove reference to the MseI SNP, thereby alleviating this rejection. Applicants traverse the statement that the invention is unpredictable. As noted above, the specification provides clear guidance as to how one skilled in the art would practice the invention.

Applicants assert that claims 1-3, 7-11, 14, 16-20, 26-29, 36-28, 40, 41, 45, 49, 54 and 55 are enabled by the specification provided. Applicants therefore respectfully request reconsideration and the withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

III. Claim Rejections- 35 U.S.C. § 102

Claim 40 stands rejected as being anticipated by Rothschild et al, U.S. Patent No: 5,374,526.

Applicants have cancelled claim 40, thereby alleviating this rejection.

IV. Conclusion

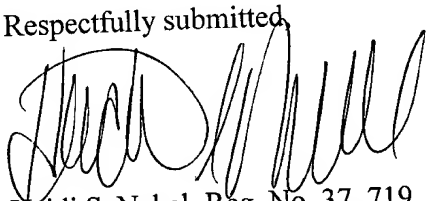
In light of the above amendments and remarks, Applicants respectfully assert that claims 1, 3-17 and 26-27 are now in condition for allowance. Applicants respectfully request

reconsideration and withdrawal of the above rejections. If it is felt that it would aid in prosecution, the Examiner is invited to contact the undersigned at the number indicated to discuss any outstanding issues.

No fees or extensions of time are believed to be due in connection with this amendment; however, consider this a request for any extension inadvertently omitted, and charge any additional fees to Deposit Account No. 26-0084.

Reconsideration and allowance is respectfully requested.

Respectfully submitted,



Heidi S. Nebel, Reg. No. 37, 719
McKEE, VOORHEES, & SEASE
801 Grand Avenue, Suite 3200
Des Moines, Iowa 50309-2721
Phone No. (515) 288-3667
Fax No. (515) 288-1338
CUSTOMER NO:

Attorneys of Record

RH

Amendments to the Claims

Claim 1 (Currently amended): A method for screening animals to determine those more likely to produce larger litters comprising:

obtaining a sample of genetic material from said animal; ~~and~~

assaying for the presence of a genotype in the prolactin receptor gene sequence as set forth in SEQ ID NO: 3 or a region thereof in said sample, wherein said genotype is comprised of a polymorphism in the prolactin receptor gene ~~said polymorphism is~~ associated with increased litter size; and

characterizing said animal.

~~selecting an animal possessing a nucleic acid sequence having at least 95% sequence identity to a region of the gene set forth in SEQ ID NO: 3 or a fragment thereof.~~

Claim 2 (Original): The method of claim 1 wherein said step of assaying is selected from the group consisting of: restriction fragment length polymorphism (RFLP) analysis, heteroduplex analysis, single strand conformational polymorphism (SSCP), denaturing gradient gel electrophoresis (DGGE) and temperature gradient gel electrophoresis (TGGE).

Claim 3 (Previously Presented): The method of claim 1 wherein said step of assaying for the presence of said polymorphism comprises the steps of:

digesting said genetic material with said restriction enzyme that cleaves the prolactin receptor gene in at least one place;

separating the fragments obtained from said digestion;

detecting a restriction pattern generated by said fragments; and

comparing said pattern with a second restriction pattern for the pig prolactin receptor gene obtained by using said restriction enzyme, wherein said second restriction pattern is associated with increased litter size.

Claim 4 (Withdrawn): The method of claim 3 wherein said restriction enzyme is AluI.

Claim 5 (Withdrawn): The method of claim 3 wherein said restriction enzyme is HinFI.

Claim 6 (Withdrawn): The method of claim 3 wherein said restriction enzyme is HypCH4IV.

Claim 7 (Cancelled)

Claim 8 (Original): The method of claim 1 wherein said animal is a pig.

Claim 9 (Original): The method of claim 3 wherein said separation is by gel electrophoresis.

Claim 10 (Original): The method of claim 3 wherein said step of comparing said restriction patterns comprises identifying specific fragments by size and comparing the sizes of said fragments.

Claim 11 (Previously Presented): The method of claim 3 further comprising, prior to said digestion step, amplifying said gene or a portion thereof with a forward primer and a reverse primer.

Claim 12 (Withdrawn): The method of claim 3 wherein said polymorphism is a polymorphic AluI restriction site.

Claim 13 (Withdrawn): The method of claim 3 wherein said polymorphism is a polymorphic HinFI restriction site.

Claim 14 (Cancelled)

Claim 15 (Withdrawn): The method of claim 3 wherein said polymorphism is a polymorphic HypCH4IV restriction site.

Claims 16 (Currently Amended): The method of claim 3 ~~12~~ wherein said restriction site is located in the 3′ coding region of the pig prolactin receptor gene.

Claim 17 (Currently Amended): The method of claim 3 ~~13~~ wherein said restriction site is located in the region between exons 8 and 9 of the prolactin receptor gene.

Claim 18 (Cancelled)

Claims 19 (Original): The method of claim 3 ~~15~~ wherein said restriction site is located in the region between exons 8 and 9 of the prolactin receptor gene.

Claim 20 (Currently Amended): The method of claim 11 wherein said forward and reverse sequence primer is capable of amplifying a region of said pig prolactin receptor gene which contains a polymorphic AluI, HinFI, or HypCH4IV~~, or MseI~~ site.

Claim 21 (Withdrawn): The method of claim 20 wherein said forward and reverse primers are selected from and based upon SEQ ID NO: 3.

Claim 22 (Withdrawn): The method of claim 20 wherein said primers are SEQ ID NO: 4 and SEQ ID NO: 5.

Claim 23 (Withdrawn): The method of claim 20 wherein said primers are SEQ ID NO: 6 and SEQ ID NO: 7.

Claim 24 (Withdrawn): The method of claim 22 wherein said forward primer is selected from the group consisting of SEQ ID NO: 1 and SEQ ID NO: 6 and said reverse primer is selected from the group consisting of SEQ ID NO: 2 and SEQ ID NO: 7.

Claim 25 (Withdrawn): The method of claim 22 wherein said primer set comprise SEQ ID NO: 1 and SEQ ID NO: 2.

Claim 26 (Currently Amended): The method of claim 20 wherein said primers are selected from the group consisting of SEQ ID NO: 8 and 9; and SEQ ID NO: 10 and 11~~; and SEQ ID NO: 12 and 13~~.

Claim 27 (Currently Amended): A method for identifying a genetic marker for litter size in animals comprising the steps of:

breeding male and female animals of the same breed or breed cross or derived from similar genetic lineages;

determining the number of offspring produced by each female animal;

determining the polymorphism in the prolactin receptor gene as set forth in SEQ ID NO: 3 of each female animal; and

associating the number of offspring produced by each female animal with said polymorphism thereby identifying a polymorphism for pig litter size.

Claim 28 (Original): The method of claim 27 further comprising the step of selecting animals for breeding which are predicted to have increased litter size by said marker.

Claim 29 (Currently Amended): The method of claim 27 wherein said analysis comprises digestion of PCR amplified DNA with the restriction enzyme selected from the group consisting of AluI, HinFI, and HypCH4IV~~, and MseI~~.

Claim 30 (Cancelled)

Claim 31 (Cancelled)

Claim 32 (Cancelled)

Claim 33 (Cancelled)

Claim 34 (Cancelled)

Claim 35 (Withdrawn): A DNA sequence from the pig prolactin receptor gene 3' translated and nontranslated region, said sequence consisting of SEQ ID NO: 3.

Claim 36 (Previously Presented): A method for screening pigs to determine those more likely to produce larger litters, and/or those less likely to produce larger litters, which method comprises of the steps:

determining the alleles of prolactin receptor present in a pig having SEQ ID NO: 3;

determining the alleles of other markers for genes known to affect litter size; and

selecting for animals with favorable combinations of alleles and against those carrying unfavorable combinations.

Claim 37 (Currently Amended): The method of claim 36 wherein the determination of prolactin receptor alleles comprises determining the presence of at least one allele associated with at least one DNA marker linked either directly or indirectly to a region of the gene set forth in SEQ ID NO: 3 ~~or a fragment thereof~~.

Claim 38 (Original): The method as claimed in claim 36 wherein the DNA marker is a microsatellite.

Claim 39 (Withdrawn): The method as claimed in claim 36 wherein the DNA marker is SW1305, S0077, S0006, SW2411, SW1035 and S0111.

Claim 40 (Cancelled)

Claim 41 (Cancelled)

Claim 42 (Withdrawn): The method of claim 41 wherein said forward primer is SEQ ID NO: 1 and said reverse primer is SEQ ID NO: 2.

Claim 43 (Withdrawn): The method of claim 41 wherein said forward primer is SEQ ID NO: 8 and said reverse primer is SEQ ID NO: 9.

Claim 44 (Withdrawn): The method of claim 41 wherein said forward primer is SEQ ID NO: 10 and said reverse primer is SEQ ID NO: 11.

Claim 45 (Cancelled)

Claim 46 (Withdrawn): The method of claim 40 wherein said marker is AluI.

Claim 47 (Withdrawn): The method of claim 40 wherein said marker is HinFI.

Claim 48 (Withdrawn): The method of claim 40 wherein said marker is HypCH4IV.

Claim 49 (Cancelled)

Claim 50 (Withdrawn): The method of claim 40 wherein said restriction fragment pattern is characterized by a 124 bp fragment, a 110 bp fragment, a 79 bp fragment, a 77 bp fragment, and a 67 bp fragment.

Claim 51 (Withdrawn): The method of claim 40 wherein said restriction fragment pattern is characterized by a 103 bp fragment, an 86 bp fragment, and a 17 bp fragment.

Claim 52 (Withdrawn): The method of claim 40 wherein said restriction fragment pattern is characterized by the pattern as shown in Figure 7.

Claim 53 (Withdrawn): The method of claim 40 wherein said restriction fragment pattern is characterized by a 281 bp fragment and a 140 bp fragment.

Claim 54 (Currently Amended): A method for identifying a marker correlated with litter size comprising the steps of:

obtaining a sample of genetic material from an animal, said sample comprising a prolactin

receptor gene as set forth in SEQ ID NO: 3;

assaying said prolactin receptor gene presented in said sample for a polymorphism;

correlating whether a statistically significant association exists between said polymorphism and litter size in an animal of a particular breed, strain, population, or group whereby said animal can be characterized for said marker.

Claim 55 (Previously Presented): The method of claim 54 wherein said animal is a pig.